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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,892	11/26/2007	Antti Haapalinna	06267.0132	4440

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EXAMINER	
RAO, SAVITHA M	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,892	HAAPALINNA ET AL.	
	Examiner	Art Unit	
	SAVITHA RAO	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03/22/2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) *3-6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/22/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/22/2010 has been entered.

Claims 1-6 are pending. Claims 3-6 remain withdrawn from consideration by the Examiner, 37 CFR 1.142(b), as drawn to non-elected inventions. Claims 1 and 2 drawn to a method for inhibiting the development of epilepsy comprising administering the alpha2-adrenoceptor antagonist atipamezole remains the subject matter under consideration.

Applicants' arguments, filed 03/22/2010, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 2 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting the development of severe epilepsy in patients at risk of developing epilepsy due to head trauma, brain ischemia, infection or neurosurgical operation with the selective α_2-adrenoceptors antagonist atipamezole, does not reasonably provide enablement for the method of inhibiting the development of epilepsy in patients at risk of developing epilepsy with any α_2-adrenoceptors antagonist. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

All of the *Wands* factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of invention and breadth of claims:

Claim 1 is drawn a method for inhibiting the development of epilepsy in patients at risk of developing epilepsy caused due to head trauma, brain ischemia, infection or neurosurgical operation by administration an effective amount of α_2-adrenoceptors antagonist. The breadth of the claim is extensive as it encompasses many different drugs which possess α_2-adrenoceptors antagonist activity including non-specific α_2-adrenoceptor antagonists.

Relative skill of those in the art:

The relative skill of those in the art is high at least a MS or PhD level in the area of neurology.

State of the prior art/Predictability or unpredictability of the art:

The α_2-adrenoceptor antagonists include both specific and non-specific α_2-adrenoceptors antagonist. Prior art teaches that non specific α_2-adrenoceptors antagonist, such as idozoxan and yohimbine, were known to facilitate epileptogenesis. I.e., cause epilepsy. (Gellman R.L et al., *J. Pharmacol. Exp. Ther.* (1987), 241 (3): 891-8, referenced in the instant IDS) which is inapposite to the instant invention. As such, the predictability of non-specific α_2-adrenoceptor antagonists working to inhibit the development of epilepsy is very low.

Amount of guidance/Existence of working examples:

The only examples present in the instant specification are for specific α_2-adrenoceptor antagonist atipamezole and no examples of the practice of the instantly claimed invention with non-specific α_2-adrenoceptors antagonists are provided. Lack of

a working example is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164.

Thus, the specification fails to provide clear and convincing evidence in sufficient support for using the claimed compounds in the method claimed.

Genetech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors as discussed above, e.g., the amount of guidance provided and the lack of working examples to practice the claimed invention herein a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pitkanen et al. (Epilepsia, Volume 44, supplement 9, 2003, pages 261-262, referenced in the instant IDS) and Puurunen et al. (Neuropharmacology 40 (2001) 597-606 already of record), in view of Ginsberg et al (Stroke, 1989; 20, pages 1627-1642, already of record)

Pitkanen et al. teach that stimulation of α_2-adrenoceptors delays the development of rekindling, a model of epileptogenesis in humans, and further teach that blocking α_2-adrenoceptors is proconvulsant, but has beneficial effects on somatomotor recovery after experimental stroke. Pitkanen et al. disclose a study they conducted to investigate whether or not atipamezole, a selective α_2-adrenoceptors antagonist, affects the recovery process from status epilepticus-induced brain trauma, which affects the

risk of epileptogenesis (page, 261, abstract 2-248, Rationale). Pitkanen et al. conclude that the data from their studies indicated that prolonged treatment with atipamezole does not totally prevent epileptogenesis; however it produced a clear disease-modifying effect; that is, the epilepsy that develops is milder and nonprogressive (page, 262, abstract 2-248, conclusions).

Puurunen et al. disclose that systemic administration of atipamezole facilitates recovery following transient focal cerebral ischemia in rats (abstract). Puurunen et al. disclose that atipamezole rapidly penetrates the brain and increases the release of central noradrenaline. Puurunen et al. also disclose that atipamezole is a potent alpha2-adrenoceptor antagonist with a high alpha2/alpha1 selectivity ratio with negligible affinity for other receptors, such as 5-HT and imidazoline receptors (page 598, left col., 2nd paragraph). Puurunen et al. disclose brain ischemic induction in rats and treatment of these rats with atipamezole hydrochloride in sterile water administered once a day (1 mg/kg subcutaneously), beginning on day 2 of the ischemic induction and continuing for 10 days (page .598, methods, sections 2.1 and 2.2). Puurunen et al. disclose atipamezole is well –tolerated over a wide range of doses and that atipamezole improved behavioral performance of ischemic rats. Accordingly, the reference provides a promising pharmaceutical approach to facilitate the recovery process following cerebral ischemia (page 604, right col., last paragraph).

Neither Puurunen nor Pitkanen et al. teaches the administration of atipamezole to **human patients** at risk of developing epilepsy.

However, animal testing in biomedical research is used as a reflection of the final outcome in humans. As disclosed by Ginsberg et al., the use of physiologically regulated, reproducible animal models is crucial to the study of ischemic brain injury, both the mechanisms governing its occurrence and potential therapeutic strategies (abstract). Ginsberg additionally teaches that rodent species are readily available at low cost and are widely employed for this purpose (abstract). In addition, Ginsberg teaches that Rodents have close resemblance to the cerebrovasuclar anatomy and physiology of higher species (page 1627, right col., 1st paragraph). Accordingly, it would have been obvious to an ordinarily skilled artisan to extrapolate the results obtained by Puurunen et al. and Pitkanen et al., which clearly recite the beneficial effects of atipamezole as a promising pharmaceutical approach to facilitate the recovery process following cerebral ischemia or epilepticus-induced brain trauma in rats, to that of mammals, and specifically humans, and, as such, develop a method of treating human patients at risk of developing epilepsy with atipamezole. An ordinarily skilled artisan will be imbued with at least a reasonable expectation of success that such a method would provide an alternative and potentially better therapeutic treatment procedure for patients at risk of developing epilepsy.

In view of the foregoing references, the instantly claimed method for inhibiting the development of epilepsy by administering an effective amount of the α_2-adrenoceptor antagonist atipamezole to a human patient at risk of developing epilepsy caused by head trauma, brain ischemia, infection or neurosurgical operation, would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made.

Pitkanen et al. explicitly teach that prolonged treatment with atipamezole to patients with status epilepticus-induced brain trauma which affects the risk of epileptogenesis, produces a clear disease-modifying effect wherein the epilepsy that develops is milder and nonprogressive. Puurunen et al. disclose atipamezole-improved behavioral performance of ischemic rats and, accordingly, provide a promising pharmaceutical approach to facilitate the recovery process following cerebral ischemia. Accordingly, both Pitkanen et al. and Puurunen et al., supported by teachings of Ginsberg et al., provide an ordinarily skilled artisan ample motivation to utilize atipamezole in treatment of a human patient with brain ischemia or status-epilepticus induced brain trauma both of which render the human at risk of developing epilepsy. An ordinarily skilled artisan will be imbued with at least a reasonable expectation of success such a method would provide therapeutic results for patients at risk for epilepsy from the prior art teachings that atipamezole helps to inhibit progression of epilepsy, decreases the intensity of epilepsy and further helps in the recovery process following cerebral ischemia or trauma.

Response to applicant's arguments filed on 03/22/2010:

In light of the new grounds of rejection above, the arguments submitted on 03/22/2010 which was for the previously submitted rejection are moot.

Conclusion

Claims 1and 2 are rejected. No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7 am to 4 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA RAO/
Examiner, Art Unit 1614

/Phyllis G. Spivack/
Primary Examiner, Art Unit 1614
May 9, 2010